REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

Claims 22 and 25 are amended herein. New claims 35-38 are added. Basis for the amendments and new claims may be found throughout the specification and claims as-filed, especially at page 13, lines 9-10, 11, and 17-18; and page 14, lines 7-8. Thus, no prohibited new matter is submitted herewith. Applicants reserve the right to file at least one continuation application directed to any subject matter deleted herein.

Specification

The Office requests that the specification be updated to reflect the status of all parent applications. This amendment to the specification updating the status of the parent matters is submitted herewith.

Objection to the claims

Claim 25 stands objected to, as "cytomegalovirus" is purportedly misspelled. Claim 25 is amended herein to address the formality. Applicants request that this objection be withdrawn.

Claim Rejections Under 35 U.S.C. § 102

Claims 22, 25 and 27-30 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Bout et al. (European Patent No. 707 071) ("Bout").

Applicants submit that Bout fails to recite every element of the presently claimed invention, especially as amended herein. To anticipate a claim, a single prior art reference must teach each and every element of the claimed invention. *See* M.P.E.P. § 2131; *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); *Hybritech Inc.v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986).

Claim 22 is amended herein to recite that the E3 sequences encoding functional 14.5K and 10.4K proteins are the only E3 sequences remaining in the adenovirus vector. Claim 22 is further amended herein to recite that the retained E3 sequences are located in place of the native E3 region and in sense orientation relative to the direction of transcription of the E3 region in the native context.

In contrast, Bout discloses E1-deleted adenoviral vectors having at least a functional part of the E3 region retained (*see* page 3, lines 32-33). However, Bout does not disclose which part of the E3 region should be retained to provide protection against an inflammation condition.

In fact, Bout discloses that the entire E3 region should be retained. In support, Applicants refer to the following passages in Bout: page 3, line 52 recites: "we constructed adenoviruses in which the E3 region is retained"; page 3, lines 55-57, recites: "recombinant vectors containing E3 are superior to vectors that are E3-deleted"; page 4, lines 7-8, recites: "such adverse effects might be prevented by using recombinant adenovirus vectors that are E1 deleted, but that retain the E3 region"; page 4, lines 26-27 recites "Accordingly, we have constructed recombinant adenivoruses that are deleted for E1 but do contain the E3 region".

Further, the working examples of Bout disclose recombinant adenovirus vectors (*e.g.*, Ad.HIL-1a, Ad.rIL-3 and Ad. TK) that contain a wild-type E3 region (*see* on page 8, line 44). Thus, these vectors retain the entire E3 region. In addition, Bout fails to disclose that the recombinant adenovirus retains only the E3 sequences encoding the 14.5K and the 10.4K proteins. Bout further fails to disclose the location and orientation of the insertion of the retained E3 sequences.

Because Bout fails to recite each and every element of the presently claimed invention, Applicants request that this rejection be withdrawn.

Claims Rejections Under 35 U.S.C. § 103

Claims 23 and 24 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bout as applied above and further in view of Krajcsi et al. (*J. Virol.*, 1996, 70(6): 4904-4913) ("Krajcsi"). Applicants traverse.

As set forth in M.P.E.P 2142, in order to establish a *prima facie* case of obviousness, three criteria must be met, *i.e.*, (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art references must teach or suggest all the claim limitations.

Applicants submit that the two cited references, alone or in combination, fail to meet the requirements for obviousness. First, the cited reference fails to recite or even to suggest all of the elements of the presently claimed invention, as amended herein.

The presently claimed invention recites that the retained E3 sequences, encoding functional 14.5K and 10.4K proteins, be inserted in the recombinant adenovirus vector in sense orientation in place of the native E3 region.

In contrast, Bout discloses that, with regard to the role of the various proteins expressed from the adenoviral E3 region, that when in the native context will act in concert to counteract the host's immune system and, thus, protect adenovirus-infected cells. Because of this disclosure, Bout motivates the skilled skilled to retain either the entire E3 region (*i.e.*, the native context) or only the 14.7K-encoding sequences (*see* page 4, lines 30-33).

Krajcsi disclose the role of the E3-encoded 14.7K and E3-10.4K/14.5K protein complexes on TNF activation, and note that E3-14.7K and E3-10.4K/14.5K block different steps in the pathway of TNF activation. Thus, Krajcsi disclose that they "presumably" work independently to counteract TNF activation. Krajcsi fails to remedy the deficiencies of Bout, as Krajcsi provides no suggestion or disclose whatsoever of retaining the E3 gene sequences encoding 10.4K and 14.5K proteins in an adenoviral vector and to utilize this vector *in vivo* to reduce the host's inflammatory responses. Moreover, there is no disclose or veven suggestion regarding the location and orientation of the retained E3 sequences within the viral genome.

Thus, Bout and Krajcsi, in combination fail to disclose or suggest the recombinant adenoviral vectors that retain the E3 sequences encoding functional 14.5K and 10.4K proteins and nothing else, and fail to disclose or suggest what location and orientation the retained E3 gene sequences should be inserted in the vector genome. Without this information, there is no expectation of success that

insertion in place of the native E3 sequence and in sense orientation would in fact work to provide expression and biological function more efficiently than insertion in place of the E3 region in antisense orientation or in place of the E1 region.

Further, Applicants respectfully submit that unexpected results are in fact present with respect to the claimed vectors.

It is a well established legal precedent that the presence of an unexpected, advantageous or superior result is evidence of nonobviousness. *See* M.P.E.P. § 716.02(a); *In re Papesch*, 315 F.2d 381, 137 U.S.P.Q. 43 (C.C.P.A. 1963). Along these lines, it is also well established that "a greater than expected result" is evidence of nonobviousness. *See* M.P.E.P. § 716.02(a); *In re Corkill*, 711 F.2d 1496, 226 U.S.P.Q. 1005 (Fed. Cir. 1985).

It has been unexpectedly discovered that insertion of the E3 gene sequences encoding 10.4K/14.5K in place of the deleted adenoviral E3 region, and in "sense" orientation, provides a functional RID complex capable of efficiently counteracting inflammation responses. The presently claimed invention recites that the retained E3 sequences, encoding functional 14.5K and 10.4K proteins, be inserted in the recombinant adenovirus vector in sense orientation in place of the native E3 region, which allows for the unexpected abilities of the claimed vectors.

In fact, various RID-expressing constructs were tested, as disclosed in the specification. In this regard, RID (E1+) refers to insertion of the E3-10.4K/14.5K gene sequences in sense orientation in place of the deleted adenoviral E1 region, RID (E3+) refers to insertion of the E3-10.4K/14.5K gene sequences in sense orientation in place of the deleted adenoviral E3 region, and RID (E3-) referring to

insertion of the E3-10.4K/14.5K gene sequences in anti-sense orientation in place of the deleted adenoviral E3 region.

As shown in Example 1 of the present application, the RID (E3+) vector was unexpectedly found to be capable of more efficiently inhibiting Fas-induced apoptosis and TNF-induced apoptosis, as well as down-regulating EGF receptors than its counterparts RID (E3-) and RID (E1+). When administered *in vivo* to animal models that mimic Fas-mediated inflammation, the RID (E3+) vector was unexpectedly found to be capable of protecting animals injected with lethal doses of anti-Fas antibody.

In light the amendments to the claims herein and the above remarks, Applicants request that this rejection be withdrawn.

Claim 31 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Bout (EP 707 071) as applied above and further in view of Kovesdi et al. (U.S. Patent No. 5,851,806) ("Kovesdi").

Claim 31, as set forth herein, is directed to recombinant adenoviral vector, wherein at least one gene of the E2, E4, and L1-L5 regions is deleted or rendered non-functional.

As discussed above, Bout discloses recombinant adenoviral vectors retaining either the native E3 region or the portion of the E3 region encoding the 14.7K protein. Kovesdi fails to remedy the deficiencies of Bout, as Kovesdi only generally relates to multiply deficient adenoviral vectors. In Example 2, Kovesdi describes an E1, E3 and E4-deleted adenovirus vector retaining a RSV-driven 14.7 gene

sequence inserted in replacement of the native E3 region (*see* column 17, lines 21 to 33).

Thus, taken in combination, Bout and Kovesdi fail to disclose or even suggest the adenoviral vector set forth herein in claim 31, wherein the vector is multi-deleted (deleted of E1 and at least another region essential to viral growth) and retains the E3 sequences encoding functional 14.5K and 10.4K proteins in place of the native E3 region and in sense orientation.

In light of the above, Applicants request that this rejection be withdrawn.

Claims 32 and 33 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Bout as applied above and further in view of Kaplan et al. (U.S. Patent No. 6,100,086) ("Kaplan") and Kovesdi.

Claim 32 recites a recombinant Ad5 vector wherein the retained E3 sequences encoding the 10.4K and 14.5K proteins are isolated from Ad2 genome and inserted in the replacement of the native Ad5 E3 region and in sense orientation. Claim 33 further recites a multi-deleted Ad5 vector retaining said Ad2 E3 sequences as defined above. Applicants submit that the cited references, alone or in combination, fail to disclose or suggest the present invention.

Bout only provides motivation for constructing recombinant adenoviral vectors retaining either the native E3 region or the portion of the E3 region encoding the 14.7K protein. Kovesdi generally relates to multiply deficient adenoviral vectors which comprise deletions in E1, E3 and E4 regions. On the other hand, Kaplan generally relates to recombinant adenovirus vectors retaining specific portions of the E3 and E4 regions that show persistent expression of the recombinant transgene. In

one embodiment, Kaplan discloses the possibility of using chimeric adenovirus vectors comprising combinations of adenovirus DNA from different serotypes (*see* column 9, lines 43-46 and line 60). Kaplan illustrates this statement with a chimeric Ad2 vector which Ad2 genome comprises an Ad17 fiber gene (*see* column 9, lines 46-48). On this basis, the Office concluded that the skilled person would have been motivated to combine the Ad5 vector genome and the AD2 E3 sequence as described in claims 32 and 33.

Applicants traverse, and submit that the skilled artisan would not have been motivated to combine the teaching of Bout with that of U.S. Patent No. Kovesdi and Kaplan because neither of the secondary references contains any indication about the possibility of retaining the E3 sequences encoding functional 14.5K and 10.4K proteins and nothing else. Thus, the skilled artisan would not any motivation to delete or rendering non-functional the Ad5 E3 region and to insert in replacement the 14.5K and 10.4K-encoding E3 sequences isolated from the Ad2 genome. Further, none of the cited references would have provided a basis for a reasonable expectation of success, because they are silent with regard to sense orientation for inserting the retained Ad2 E3 sequences in replacement of the native Ad5 E3 region.

Applicants submit that there is no motivation to reach the recombinant adenovirus vectors of the claimed invention. Thus, Applicants request that this rejection be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

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By: _____
Deborah H. Yellin
Registration No. 45,904

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

VA 657385.1